REMARKS

The Examiner is thanked for the courtesies extended during the telephonic interview with the undersigned on June 19, 2003. During the interview, the Examiner agreed that the claims would be allowable over the art of record if claim 1 was amended to recite that the polymer matrix is covalently attached directly to the substrate.

Accordingly, Claim 1 has been amended to recite that "the polymer matrix is covalently attached directly to the substrate to provide a density of the polymer matrix on the substrate of at least 2 $\mu g/cm^2$." Support for this amendment is found in the specification at, for example, paragraphs [0006], [0012], [0018], [0029], [0051], [0054], [0058], and [0060], and in Examples 1, 2, 4, 5, 6, 7, 8, 9, and 10.

Claims 113-117 have been added. Support for these claims is found in the specification at, for example, paragraphs [0006], [0008], [0012], [0016], [0018], [0029], [0037], [0051], [0054], [0058], and [0060], and in Examples 1, 2, 4, 5, 6, 7, 8, 9, and 10.

Claims 13-16 and 33-38 were amended to depend from claim 113 and claim 30 has been amended to depend from claim 116. These amendments were necessitated by the amendment to claim 1. Support for these amendments is found in the specification at, for example, paragraphs [0006], [0012], [0018], [0029], [0051], [0054], [0058], and [0060], and in original claims 1, 13-16, 30, and 33-38. *See, In re Gardner*, 177 USPQ 396, 397 (CCPA 1973) and MPEP §§ 608.01(o) and (l).

Rejections under 35 USC § 103

Claims 1-38 were rejected under 35 USC § 103(a) as unpatentable over International Publication No. WO 92/03732 assigned to Bioprobe International, Inc. ("Bioprobe"). (Paper No. 9 at 3.) Claims 22, 24-25, and 33-34 were also rejected under 35 USC § 103(a) as unpatentable over Bioprobe in view of Döbeli, *et al.*, U.S. Patent No. 5,047,513 ("Döbeli"). (Paper No. 9 at 4.)

For the reasons set forth below, the rejections, respectfully are traversed.

Bioprobe discloses compositions and methods for preparation of assay systems, in particular, "solid phase" systems. (p. 1, lns. 7-8.) In the assay system, Bioprobe discloses "water-soluble compounds (both monomers and polymers) including hydrophobic moieties that ***bind tightly*** to, e.g., the plastics commonly used as solid phases...." (p. 3, ln. 33 - p. 4, ln. 1.) "These compounds further carry reactive functional groups (e.g., hydrazide or 2-(N-methylpyridyl) groups) which form ***stable covalent bonds with ligands*** ...." (p. 4, lns. 1-4.) Bioprobe discloses a general formula for such reagents as:

$$(R^H\text{-})_x\, A\, (\text{-}X)_y$$

wherein R^H "represents a hydrophobic moiety which develops ***substantial nonspecific interactions*** with a hydrophobic material, such as solid phase materials ...." (*Id.* at lns. 8-15.) Bioprobe further distinguishes between the type of binding between (1) the solid phase material and the coating material and (2) the coating material and the ligand:

> The desired coating material is provided in a hybrid form as a combination of (1) one or more hydrophobic moieties designed to maximize and therefore stabilize the ***nonspecific binding of the coating material with the solid phase materi ls***, and (2) reactive groups capable of forming

> ***stable covalent bonds with ligand*** of interest in a specific manner. (p. 7, lns. 1-9.)
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> This spacer serves the purpose of effectively establishing two domains in the molecule: a hydrophobic domain which ***interacts with*** the hydrophobic materials (primarily, through nonspecific binding mechanisms); and a reactive group-presenting domain, which permits the ***binding*** to specific site(s) of the ligand in readily-accessible form. (*Id.* at lns. 23-30.)
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> Polymers that ***bind tightly to plastics*** and form ***covalent bonds with the nucleophilic groups of proteins*** (e.g., – amino or SH groups) are also contemplated. (p. 11, lns. 28-31.)

Bioprobe further discloses methods for avoiding crosslinking of the polymeric materials. For example, Bioprobe discloses that "[w]hereas the direct reaction of a reactive dihydrazide (*e.g.*, adipic dihydrazide) tends to result in the formation of insoluble products (probably due to crosslinking), the addition of small amounts of hydrophobic hydrazides to the dihydrazide reaction mixture tends to ***inhibit crosslinking***, permitting a longer reaction time and a more complete reaction." (p. 10, lns. 14-21.)

In all of the Bioprobe examples, to prepare the surface of a solid phase for binding to ligands, the coating material was applied to the solid phase, optionally incubated for a period of time, and then washed off. (*See e.g.* p. 12, ln. 21 – p. 32, ln. 18.) Table 2 shows resistance to detergent (*i.e.*, Tween-20) of two different coating materials (dextran-hydrazide and dextran-phenylhydrazide) applied to polystyrene

microtiter plates. (p. 20, lns. 4-15.) At 10% Tween-20, 26.91% and 66.74% binding of rabbit anti-HRP was disclosed for the coating materials, respectively. (*Id.*)

Döbeli discloses metal chelate resins used for the purification of, *e.g.* proteins. (Col. 1, lns. 58-62.) The metal chelates have the structure of:

$$NH_2\text{-}(CH_2)_x\text{-}CH(COOH)\text{-}N(CH_2COOH)_2.$$

(Col. 2, ln. 10.)

In making both rejections, the Examiner asserted that Bioprobe discloses "an assay platform that has a coating material ... for use in assay methods involving solid phase materials (pg. 3, lines 28-32; page 4, lines 8-29; pg. 6, lines 32-35 to pg. 7, line 19) ... [that the] coating comprise a polymer such as dextran (pg. 10, lines 7-21) that a bind to the solid phase materials ... [that a] spacer is also included ... (pg. 7, lines 30-35 to pg. 8, lines 1-2; pg. 8, lines 25-35 to pg. 9, lines 1-26) ... [and that the] ligand is comprised of biologically active molecules to target molecules such as DNA and RNA (pg. 9, lines 27-35)." (Paper No. 9 at 3-4 and 4-5.)

The Examiner acknowledged, however, that Bioprobe fails to disclose that the density of the polymer matrix on the substrate is at least 2 $\mu g/cm^2$. The Examiner contented, however, that because "the polymer matrix of the reference contains all of the features required by the instant assay platform, i.e. the polymer bind to the substrate, the polymers are crosslinked to other polymers and attached to a ligand, it is inherent that the density of the polymer of the reference would also be at least 2 $\mu g/cm^2$." (*Id.* at 4 and 5.)

In making the rejection of claims 1-38, the Examiner further acknowledged that Bioprobe "differs from the claimed invention [in] failing to include the features such

as a glass substrate (Claim 11) and the ligand being a metal chelate (Claim 24)." (*Id.*) To fill this acknowledged gap, the Examiner asserted that the features of the dependent claims "are either well known alternative or constitute obvious variations ...." (*Id.* at 4.)

The Examiner concluded that "[i]t would have been obvious to ... includes [sic] these features as elements of the assay platform of Bioprobe because the polymer of Bioprobe can be used in conjunction with solid phase materials with a wide range of ligands ...." (*Id.*)

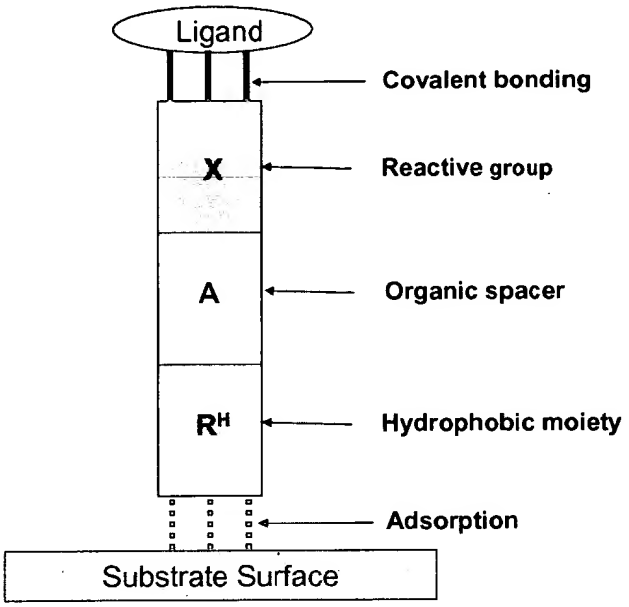
In making the rejection of claims 22, 24-25 and 33-34, the Examiner acknowledged that Bioprobe "differs from the claimed invention by failing to specifically include a metal chelate as the ligand." (*Id.* at 5.) To fill this acknowledged gap, the Examiner relied on Döbeli as disclosing "a metal chelate for chromatography purification of proteins." (*Id.*)

The Examiner then concluded that "[i]t would have been obvious ... to modify the assay platform of Bioprobe by including metal chelate as [disclosed] by Döbeli because metal chelate, especially nickel chelate, are known to have a high specificity towards biopolymers such as peptides and proteins. The substitution of the nickel chelate ligand of Döbeli as a ligand in the platform of Bioprobe would constitute a routine choice of a well known ligand ...." (*Id.*)

Our RESPONSE TO OFFICE ACTION INCLUDING AMENDMENT dated January 29, 2003 ("Previous Response") was filed concurrently with a Declaration of Dr. William Kappel under 37 CFR § 1.132 ("Declaration"). In the Declaration, Dr. Kappel demonstrates that Bioprobe does not disclose inherently, or otherwise, a density of the

polymer matrix on the substrate of at least 2 μg/cm^2 as recited in, *e.g.* claim 1. (*See* Decl., ¶¶8 and 18).

Dr. Kappel states that Bioprobe discloses ***adsorbing*** a tripartite reagent to a substrate by hydrophobic (non-covalent) interactions through the R^H portion of the reagent, and that the Bioprobe reagent may therefore be depicted as follows:



(Decl., ¶¶10-11).

Dr. Kappel demonstrates, based on well known principles of adsorption chemistry, the Bioprobe reagent, at best, forms a non-covalently bonded monolayer on such a surface. (Decl., ¶¶12-14). Dr. Kappel also demonstrates that such a non-covalently bonded monolayer would produce a maximal possible polymer density of the Bioprobe reagent on the substrate of about 300 ng/cm^2. (Decl. ¶¶15-16). Dr. Kappel also notes that the presently claimed minimal polymer matrix density, *i.e.*, "at least about

2 μg/cm^2," is more than ***six-fold higher*** than the maximal possible polymer density disclosed in Bioprobe. (Decl., ¶¶16-17).

In response to the Declaration, the Examiner asserted that the polymer "of Bioprobe is covalently attached to the substrate [e.g. '*water-soluble compounds (both monomers and polymers) including hydrophobic moieties that bind tightly to the plastic commonly used as solid phase*' (substrate) (pg. 3, lines 33-35 to page 4, lines 1-7)]. Therefore, the density of the 'polymer matrix' of Bioprobe would be at least 2 μg/cm^2." (Paper No. 9 at 7.) The Examiner then summarily dismissed the Previous Response and Declaration without any factual findings or reasoning. "It is the examiner position that the density of the 'polymer matrix' of Bioprobe would be at least 2 μg/cm^2 and the declaration is not sufficient to overcome the rejection under 35 U.S.C. 103(a) of claims 1-38 based on [Bioprobe] as discussed above." (*Id.*)

The Examiner further asserted that Bioprobe discloses dextran as a polymer and polystyrene as a solid phase. (*Id.* at 8.) The Examiner concluded that "the 'platform' of Bioprobe is obvious of the presently claimed platform. The density of the 'polymer matrix' of Bioprobe would be inherently at least 2 μg/cm^2 because the polymer and substrate material anticipates the substrate and polymer material of the presently claimed invention." (*Id.*)

Initially, we note that it is the Examiner's burden to consider all evidence and arguments presented to rebut the asserted *prima facie* case for obviousness.

> ***Office personnel should consider all rebuttal arguments and evidence presented by applicants***. See, e.g., *In re Soni*, 54 F.3d 746, 750, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995) (error not to consider evidence presented in the specification). *C.f., In re Alton*, 76 F.3d 1168, 37 USPQ2d

> 1578 (Fed. Cir. 1996) (error not to consider factual evidence submitted to counter a 35 U.S.C. 112 rejection); *In re Beattie*, 974 F.2d 1309, 1313, 24 USPQ2d 1040, 1042-43 (Fed. Cir. 1992) (Office personnel should consider declarations from those skilled in the art praising the claimed invention and opining that the art teaches away from the invention.) MPEP § 2144.08(II)(B) (8th Ed., Rev. 1, February 2003, p. 2100-147).

Moreover, the Examiner is required to reconsider all the evidence, both supporting and rebutting the *prima facie* case, and ***clearly communicate the factual findings*** that support his conclusion.

> A determination under 35 U.S.C. 103 should rest on all the evidence and ***should not be influenced by any earlier conclusion***. See, e.g., *Piasecki*, 745 F.2d at 1472-73, 223 USPQ at 788; *In re Eli Lilly & Co.*, 902 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990). Thus, ***once the applicant has presented rebuttal evidence, Office personnel should reconsider any initial obviousness determination in view of the entire record***. See, e.g., *Piasecki*, 745 F.2d at 1472, 223 USPQ at 788; *Eli Lilly*, 902 F.2d at 945, 14 USPQ2d at 1743. All the proposed rejections and their bases should be reviewed to confirm their correctness. Only then should any rejection be imposed in an Office action. ***The Office action should clearly communicate the Office's findings and conclusions, articulating how the conclusions are supported by the findings.***
>
> Where applicable, the findings should clearly articulate which portions of the reference support any rejection. Explicit findings on motivation or suggestion to select the claimed invention should also be articulated in order to support a 35 U.S.C. 103 ground of rejection. *Dillon*, 919 F.2d at 693, 16 USPQ2d at 1901; *In re Mills*, 916 F.2d 680, 683, 16 USPQ2d 1430, 1433 (Fed. Cir. 1990). ***Conclusory statements of similarity or motivation, without any articulated rationale or evidentiary support, do not constitute sufficient factual findings***. MPEP § 2144.08(III) (8th Ed., Rev. 1, February 2003, p. 2100-149) (emphasis added).

This, however, the Examiner has not done. In the "Response to Amendment" and "Response to Arguments," the rejection merely presents the kind of "conclusory statements of similarity or motivation, without any articulated rationale or evidentiary support," which are clearly prohibited by Patent Office procedure. The "examiner position" alone is simply not enough to maintain the rejections in the face of the overwhelming rebuttal evidence presented by the Applicants. The rejections are devoid of any factual findings, much less findings sufficient to refute the evidence submitted. For this reason alone the rejections are legally and factually deficient, and must be withdrawn.

It is fundamental that a *prima facie* case of obviousness must be based on facts, "cold hard facts." *In re Freed*, 165 USPQ 570, 571-72 (CCPA 1970). When the rejection is not supported by facts, it cannot stand. *Ex parte Saceman*, 27 USPQ2d 1472, 1474 (BPAI. 1993).

The rejections admit that Bioprobe does not disclose a density of the polymer matrix on the substrate as recited in, *e.g.* claim 1 and that it must rely on inherency for that element. (Paper No. 9 at 4 and 5) ("it is inherent that the density of the polymer of the reference would also be at least 2 $\mu g/cm^2$.").

However, a rejection based on inherency must provide factual and technical grounds establishing that the inherent feature necessarily flows from the teachings of the prior art. *Ex parte Levy*, 17 USPQ2d 1461, 1464 (PBAI 1990). It is not enough that the asserted inherent property may arise from the facts disclosed. *In re Oelrich*, 212 USPQ 323, 326 (CCPA 1981) (inherency must flow as a necessary conclusion from the prior art, not simply a possible one); and *Glaxo Inc. v. Novopharm*

Ltd., 34 USPQ2d 1565, 1567 (Fed. Cir. 1995) ("Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.")

The only support offered for inherency is that "the polymer matrix of the reference contains all of the features required by the instant assay platform, i.e. the polymer bind to the substrate, the polymers are crosslinked to other polymers and attached to a ligand..."

It is respectfully submitted that the assertion "the polymer bind to the substrate, the polymers are crosslinked to other polymers and attached to a ligand," without more, does not meet the evidentiary burden of coming forth with "a basis in fact and/or technical reasoning" to support the inherency reasoning. *Ex parte Levy*, 17 USPQ at 1464. The rejection offers only a conclusion, and fails to provide a factual basis or to shed any light on why, the polymer must be present on the surface of the substrate at a density of "at least 2 $\mu g/cm^2$." For this reason also the rejections are deficient, and should be withdrawn.

As is well settled, suggestion or motivation to make a combination as claimed must also be based on factual evidence. The "case law makes clear that the best defense for guarding against a hindsight-based obviousness analysis is the rigorous application of the ***requirement for a showing of a teaching or motivation to combine***" the references applied. *Ecolochem Inc. v. Southern California Edison*, 56 USPQ2d 1065, 1073 (Fed. Cir. 2000); and *see In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("Combining prior art references ***without evidence*** of such a

suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together *the prior art to* defeat patentability-the essence of hindsight.").

Even when a rejection is based on a single reference, such as the rejection of claims 1-38 over Bioprobe alone, "there must be a showing of a suggestion or motivation to modify the teachings of that reference." *In re Kotzab*, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). And there also "***must be evidence*** that a skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, ***would select*** the elements from the cited [reference] for combination in the manner claimed." *Ecolochem Inc. v. Southern California Edison*, 56 USPQ2d at 1076 (*citing In re Rouffet*, 47 USPQ2d 1453, 1456 (Fed. Cir. 1998)).

Here, neither Bioprobe alone nor Bioprobe in combination with Döbeli suggest or provide a motivation to use a polymer density on a substrate of "at least 2 $\mu g/cm^2$" as claimed. Rather, when considered as a whole, Bioprobe discloses anchoring the reagent to a substrate by adsorption. Using the adsorption mechanism as disclosed in Bioprobe, however, Dr. Kappel demonstrates that achieving the "at least 2 $\mu g/cm^2$" as claimed is not possible. And, the Examiner has provided no evidence or technical reasoning to explain why one would depart from the Bioprobe method for anchoring the reagent to a substrate surface. Nor does the Examiner explain with evidence or technical reasoning why the density of polymer on the substrate surface that is achieved, approximately 300 ng/cm^2, should be modified, let alone modified to the specific density recited in the claim - "at least 2 $\mu g/cm^2$." For this additional reason, the rejections are deficient and should be withdrawn.

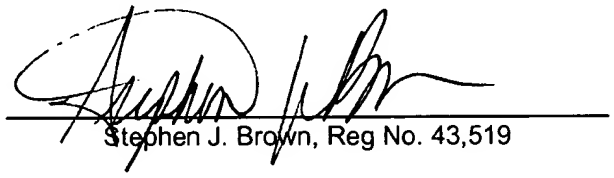
We further note that the data in Tables 2 and 3 of Bioprobe (pp. 20-21) demonstrate that a significant percentage of Bioprobe reagent is washed off the substrate with detergent. This would not be expected to occur if the Bioprobe reagent were covalently bonded to the substrate.

We also note that the Examiner is not able to identify a single citation from Bioprobe that states unequivocally that the Bioprobe reagent covalently binds to the substrate. At best the Examiner quotes "bind tightly" language from Bioprobe. But "binds tightly" is not "covalently binding." Indeed, when Bioprobe means "covalently binding" it say so explicitly, *e.g.* when describing the binding of the reactive functional group to a ligand. *See* page 4, lines 1-5 ("These compounds further carry reactive functional groups ... which form stable covalent bonds with ligands at specific sites on the ligands ...."). Thus, the Examiner's position is factually untenable.

Notwithstanding the foregoing, claim 1 has been amended for the purposes of clarity as requested by the Examiner, to recite that the polymer matrix is covalently attached directly to the substrate. And, claim 117 is also presented, which clearly recites that the polymer matrix is covalently bonded to the substrate, which is simply not shown or suggested, inherently or otherwise, in Bioprobe.

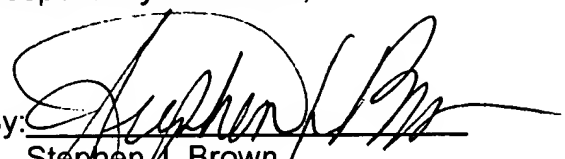
For the reasons set forth above, entry of the amendments, withdrawal of the rejections, and allowance of the claims are respectfully requested. If the Examiner has any questions regarding this paper, please contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on August 4, 2003.



Stephen J. Brown, Reg No. 43,519

Respectfully submitted,



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